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Ecology and metabolism of the beneficial intestinal commensal bacterium *Faecalibacterium prausnitzii*

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Faecalibacterium prausnitzii is a major commensal bacterium, and its prevalence is often decreased in conditions of intestinal dysbiosis. The phylogenic identity of this bacterium was described only recently. It is still poorly characterized, and its specific growth requirements in the human gastrointestinal tract are not known. In this review, we consider *F. prausnitzii* metabolism, its ecophysiology in both humans and animals, and the effects of drugs and nutrition on its population. We list important questions about this beneficial and ubiquitous commensal bacterium that it would be valuable to answer.

Introduction

Faecalibacterium prausnitzii is a member of the phylum Firmicutes and a major component of human microbiota, but was first described only recently.[1] It has been the subject of few studies, partly because it is an extremely oxygen-sensitive (EOS) bacterium.[1] It is an atypical bacterium that has been difficult to classify in the bacterial nomenclature.[1] Analysis of the *F. prausnitzii* membrane suggests that this bacterium either lacks cell wall lipopolysaccharides (LPS) or displays an unusual LPS composition.[2] Over the last ten years, there has been substantial interest in *F. prausnitzii* in the microbiota of patients with intestinal and metabolic disorders, and particularly Inflammatory Bowel Disease (IBD) patients. These diseases are characterized by a dysbiosis, or in other words microbial imbalance (between "symbionts" and "pathobionts"), in the gut.[3] The Firmicutes-Bacteroidetes ratio is commonly affected with a decrease of *F. prausnitzii* population in such patients.[4] Recent studies report an association between low *F. prausnitzii* population levels and the risk of relapse in IBD. In ulcerative colitis (UC) patients, there is a clear correlation between *F. prausnitzii* population level and maintenance of clinical remission.[5] Similarly, in Crohn disease (CD) patients, a low relative count of this bacterium is risk factor for endoscopic recurrence within 6 months.[6] Interestingly, *F. prausnitzii* has immunomodulatory properties and is now considered as both an indicator of, and an actor in, human health in adults.[7] Although there have been various suggestions for the mechanisms involved, the role of *F. prausnitzii* in host immune responses is poorly understood. Human *F. prausnitzii* strains have been classified into two different molecular phylogroups, but no functional specificities have been linked to these phylogroups (**Fig. 1**).[8] Genomic data generated by microbiota metagenome projects will undoubtedly improve our knowledge of non-cultivable and difficult to cultivate strains. It may also be very informative to study the anti-inflammatory activities and molecular phylogroups of strains isolated from IBD patients and compare them to those of strains isolated from healthy individuals.

The role of *F. prausnitzii* in the homeostasis of the crosstalk between host and microbiota is unlikely to be restricted to its anti-inflammatory potential.[6] Indeed, the biological effects of *F. prausnitzii* may be also linked to its localization in the gastrointestinal tract (GIT), its metabolic activities, and its complementarities with other bacteria of the microbiota. In this review, we consider where and when *F. prausnitzii* may affect host physiology. Various unresolved questions that we believe important are listed in **Figure 1**. We also propose an approach to develop a novel personalized treatment strategy based on using medicine and nutrition to modulate the *F. prausnitzii* population.

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F. prausnitzii: A Late but Major Commensal Colonizer of the GIT

F. prausnitzii is usually described as an EOS bacterium but is able to grow in micro-aerobic conditions by using extracellular electron transfer in the presence of flavins and cysteine or glutathione.[1,9] This capacity may explain how such anaerobic bacteria could colonize niches, including the gut mucosa, where there is an oxygen gradient.[9,10] Nevertheless, it is difficult to cultivate *F. prausnitzii*, and various molecular approaches have been used to evaluate *F. prausnitzii* populations: (1) detection of 16S rRNA gene sequences,[11,12] (2) PCR techniques based on single primers,[13,14] (3) assaying 16S RNA by membrane-array methods[15]

or hybridization techniques, and (4) in situ hybridization.[16,17] *F. prausnitzii* DNA was found in the recently described metagenome catalog and is now considered to be a major member of the phylogenetic core.[18,19] The abundance and ubiquity of *F. prausnitzii* suggest that it is a major contributor to microbiota functions in healthy individuals. It is therefore important to determine both the kinetics of its implantation and its localization in the GIT.

Main questions still unresolved:
- **Is there an association between *F. prausnitzii* phylogroups and particular functional capacities?**
- **What is the ecological niche of *F. prausnitzii* outside the gut?**
- **What are the factors that allow commensal *F. prausnitzii* strains to colonize the intestine and survive so successfully in this niche?**
- **What are the best methods for the diagnosis of *F. prausnitzii* dysbiosis in routine clinical practice?**
- **What contribution does the butyrate produced by *F. prausnitzii* make to host health?**
- **What are the beneficial mechanisms and roles of *F. prausnitzii* that are absent from the microbiota during dysbiosis?**
- **What is the best way to treat and/or prevent IBD that is associated with *F. prausnitzii*-linked dysbiosis?**

Figure 1. Main questions still unresolved about *F. prausnitzii*.

Temporal colonization in humans (Fig. 2)

Although *F. prausnitzii* is dominant in healthy adults, its population in the intestine is modulated by diverse factors. A recent study suggests that the amount of *F. prausnitzii* in the gut microbiota depends on the sex of the host: there is less in human females than males (female to male ratio: 0.41, $P \leqslant 0.05$ as evaluated from gut microbiota DNA).[20] Several reports indicate that the populations of this bacterium change with age. The amount of *F. prausnitzii*-specific RNA in stools from babies up to the age of 6 months is below the detection threshold; the value then increases between ages 6 and 24 months but remains low until early childhood (2–3 years).[21-24] In elderly persons, there is a significant decrease of *F. prausnitzii* to 0.3%.[25] The low *F. prausnitzii* populations in early infancy suggest that the arrival of initial colonizers may facilitate subsequent implantation of *F. prausnitzii*. Possibly, consumption of the available oxygen by facultative anaerobic bacteria is required to generate an anaerobic environment favorable for the growth of obligatory anaerobic bacteria such as *F. prausnitzii*.[26] The implantation of EOS bacteria and specifically *F. prausnitzii* depends on the physico-chemical conditions previously created by other commensal bacteria.[27] Rezzonico et al. found that after inoculation of germ-free mice with a simplified human microbiota, all tested strains were systematically detected in all animals except for the reference strain of *F. prausnitzii* A2–165 (DSM17677).[28] In these experiments, all bacteria were introduced at the same time, and this did not allow efficient implantation of *F. prausnitzii*. A recent study describes *F. prausnitzii* in mono-colonized recipient germ-free mice,[29] but we have been unable to obtain rats mono-colonized by *F. prausnitzii*: prior colonization by *Bacteroides thetaiotaomicron* was required for robust implantation of *F. prausnitzii* in a rat model.[30] After 4 weeks of preparation of the GIT by *B. thetaiotaomicron*, a stable balance was maintained between the two bacteria, with *B. thetaiotaomicron* counts remaining 100-fold higher than *F. prausnitzii* counts.[30] These investigations with various rodent models maintained in germ-free conditions suggested that oxygen tension is an important determinant of colonization of the gut by *F. prausnitzii*. According to the "oxygen hypothesis" proposed by Rigottier-Gois,[31] oxygen is a major factor shaping patterns of colonization by EOS gut microbes. These observations provide insights into mechanisms governing microbial ecology and processes of colonization; they also raise questions about the ecological niche of the various strains outside the GIT (**Fig. 1**).

Colonization along the human GIT

F. prausnitzii implantation varies along the GIT, with a significantly higher population in the proximal colon than in the terminal ileum,[32] and few differences have been observed between the numbers of this organism in different parts of the large bowel. Relatively little is known about the interaction of *F. prausnitzii* with the mucus layer produced by the intestinal epithelium. Because of its distribution in the GIT, *F. prausnitzii* has been called a "fecomucus" bacterium: the highest concentration is in feces, and it is less abundant but detectable in mucus.[33,34] *F. prausnitzii* can survive in the adjacent mucosa where there is an oxygen influx from the gut epithelium. Inside the gut, its growth and survival (at the oxygenated fecal-mucosal interface) seems to depend on extracellular redox mediators such as flavin.[9,10] Thus, the distribution of *F. prausnitzii* along the longitudinal and luminal axes of the gut are determined by a combination of several environmental factors, including the distribution of redox mediators, oxygen concentration, other bacteria, the mucus layer, bile salt concentrations, and pH.[8,35] In rats, *F. prausnitzii* implantation is in part dependent on the same factors and it contributes to intestinal homeostasis mainly through effects on cell differentiation, and especially that of cells of the secretory lineage.[30] A better understanding is required of the environmental factors allowing the survival and the growth of *F. prausnitzii* in the gut (**Fig. 1**).

***F. prausnitzii* in animal intestinal microbiota**

F. prausnitzii is widely distributed in the GIT of mammals. Interestingly, in pigs, FISH analyses showed that the localization of *F. prausnitzii*-related bacteria is very similar to that in humans. It is abundant in the hind gut (proximal colon 2 ± 0.5% and rectum 2.4 ± 0.7% of dominant bacteria) but was below the detection threshold in both the stomach and jejunum.[36] *F. prausnitzii* has been detected in the microbiota of pigs and piglets,[37,38] calves,[39] poultry including chickens and turkeys,[40-46] and mice.[47] Most

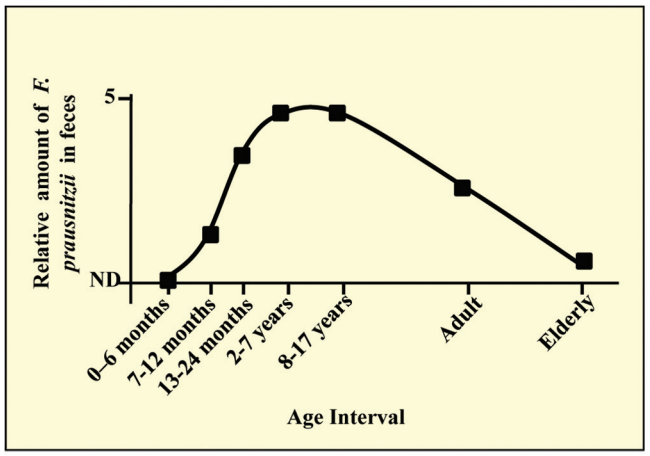

Figure 2. Kinetics of implantation of *F. prausnitzii*. Changes in human fecal *F. prausnitzii* populations with host age (adapted from Hopkins et al., Balamurugan et al. and Van Tongeren et al.).[21,22,25]

of these strains share less than 97% sequence identity with the human strain in the 16S rRNA gene and are thus named *F. prausnitzii*-like strains.[36,40-42] They are predominant bacteria in the intestines of many mammals and also in some insects. Indeed, under its initial name of *Fusobacterium prausnitzii*, *F. prausnitzii* has been found in the hind gut of the cockroach *Eublaberus posticus*.[48] These descriptions have led some authors to suggest that each animal species has its own distinctive set of phylotypes related to *F. prausnitzii* in its GIT.[41]

What is Known about *F. prausnitzii* Metabolism?

Human *F. prausnitzii* has been considered to be "a key functional member of the core microbiome that most influences host metabolism and hence health".[49] This role is in part due to *F. prausnitzii* being one of the most abundant of the butyrate-producing bacteria in the GIT. However, it is not known whether it is the major butyrate producer of the intestinal microbiota. Butyrate is a short chain fatty acid (SCFA) and very important in gut physiology and in the systemic functions and beneficial effects of the gut microbiota for human health.[50] Analysis of SCFAs pattern in stools from CD patients shows higher than normal proportions of acetate (70%) and low proportions of propionate and butyrate (14.9% and 7.99%, respectively).[51] However, it is not yet clear whether the production of butyrate by *F. prausnitzii* is directly linked to host responsiveness or health benefits. It would be informative to construct *F. prausnitzii* mutants defective for butyrate synthesis and use them to evaluate the effect of butyrate produced directly in situ by *F. prausnitzii* (**Fig. 1**). The metabolic activity of *F. prausnitzii* is not restricted to the production of butyrate, and its potential for immunomodulation is also linked to other molecules and/or metabolites, but they have not yet been characterized (**Fig. 1**).[6]

The production of SCFA by *F. prausnitzii* was described in vitro for the first time by using a complex rumen fluid-based medium in strict anaerobic conditions.[52] *F. prausnitzii* is an acetate consumer and butyrate producer, and it can also produce carbon dioxide, formate, and D-lactate, although none of the strains isolated to date produce hydrogen.[1,53] In batch cultures, most of the carbon in the butyrate produced (around 85%) is derived from external acetate, with only 15% provided directly from glucose.[54] In 2002, Duncan et al.[55] detected a Butyryl CoA:acetate CoA transferase in the *F. prausnitzii* reference strain A2-165 in which no butyrate kinase activity was found. In the human GIT, *F. prausnitzii* produces butyrate associated with a consumption of both acetate and carbohydrates.[52,54] Moreover, *F. prausnitzii* strains can hydrolyze fructose, fructo-oligosaccharide, apple pectin, and starch, and some can hydrolyze inulin.[1,8,56] None of the strains isolated to date are able to exploit as sole energy source any of arabinose, melibiose, raffinose, rhamnose, ribose, xylose, linear and α-1,2-branched dextrans, arabinogalactan, xylan, citrus pectin, or peptides.[1,8,57] Most *F. prausnitzii* strains can grow on the host-derived sugar *N*-acetylglucosamine and some strains on D-glucosamine and D-glucuronic acid; B-glucuronidase activity has been reported in some *F. prausnitzii* isolates.[8,58] This suggests that *F. prausnitzii* is able to switch from diet- to host-derived substrates, a feature common to several major bacterial species in the human colon.[59,60] No evidence has been found of porcine gastric mucin fermentation by *F. prausnitzii*.[8] No minimal medium has yet been described for *F. prausnitzii* growth although some strains are able to grow on simplified medium containing acetate.[1] The analysis of the metabolomic profiles of a large collection of strains isolated from both healthy subjects and patients suffering disease-associated dysbiosis would be very useful, in particular to document the metabolic activity of *F. prausnitzii*.

How Medicines and Nutrition May Modulate *F. prausnitzii* Population and Activity

Various treatments used for IBD patients, such as rifaximin,[61] interferon-α-2b,[62] cortisol, and infliximab,[33] have been shown to have a positive effect on the *F. prausnitzii* population in the microbiota. However, there is published evidence that a large number of xenobiotics may decrease the *F. prausnitzii* population in the microbiota. Antibiotic therapy, chemotherapy, isoflavones, and essential oils markedly decrease the richness of species of the *Clostridium* cluster IV and significantly reduce *F. prausnitzii* populations.[63-66]

The metabolism of colonic bacteria depends largely on fibers that are not digested by human enzymes in the upper GIT. Work with fiber-free and fiber-supplemented liquid diets found that *F. prausnitzii* populations and fecal butyrate correlate with the fiber input.[67] In vitro conditions mimicking those of the proximal colon show that high levels of dietary fiber significantly increased clostridial cluster XIVa and *F. prausnitzii* populations.[68] Other specific diets, like a raffinose diet, a chickpea diet, and a novel diet based on fibers such as polydextrose and soluble corn fiber, can increase *F. prausnitzii* abundance.[69,70] Diet may affect *F. prausnitzii* populations directly or indirectly by enhancing metabolite cross-feeding between microbes. The benefits of fiber intake have been demonstrated in a murine model of IBD, and

this work also suggested a link between fiber and *F. prausnitzii* levels.[71] However, elemental diet therapy (nutrients in an easily assimilated form essentially composed of amino acids, fats, sugars, vitamins, and minerals), used mainly in the treatment of CD patients may decrease fecal *F. prausnitzii* counts.[72] In fact, this type of diet permits only very small amounts of undigested food residues, and such residues are required for normal levels of microorganisms in the lower gut.

The effects of prebiotics, such as inulin, on bifidogenic and butyrogenic bacteria are well established. The inclusion of inulin-type fructans in the diet of obese women may affect the gut microbiota, including increases in the populations of *F. prausnitzii* species, and thereby may have a significant impact on several key metabolites involved in obesity and/or diabetes.[73] The intake of 10 g/day inulin over a 16-day period resulted in specific and significant modifications of the composition of the human microbiota characterized by an increase in both *Bifidobacterium* and *F. prausnitzii*.[74,75] Moreover, in vitro experiments showed that some exopolysaccharides produced by *Bifidobacterium pseudocatenulatum*, a human intestinal strain of Bifidobacteria, could increase the prevalence of *F. prausnitzii*.[76] Similarly, a human study showed that *B. longum* BB536 intake (13 weeks treatment) enhanced *F. prausnitzii* 16S rRNA gene copy numbers in Japanese individuals with cedar pollinosis.[77] This is consistent with a putative symbiotic cooperation or cross feeding between *F. prausnitzii* and microbes generally recognized as beneficial, such as *Bifidobacterium* and *Lactobacillus* spp.[45,46] For instance, *Bifidobacteria* are acetate producers in the gut, and one possible approach to increase the *F. prausnitzii* population is to feed *Bifidobacteria*, which then feed *F. prausnitzii* by producing acetate. However, the effects of probiotics are strain-specific. Indeed, a recent study has demonstrated that the intake of *Lactobacillus johnsonii* strain La1 by healthy volunteers decreased *F. prausnitzii* levels.[78]

The consumption of some prebiotics or probiotics could enhance the concentrations of beneficial species and especially *F. prausnitzii* in the GIT. This type of approach is promising for patients with intestinal disorders, although relevant clinical trials performed to date included only small numbers of subjects and lack statistical power. We believe that it is likely that therapeutic strategies will need to be individually adapted to the findings of microbiota analysis, as proposed by Swidsinski[33] (**Fig. 1**).

Conclusion

F. prausnitzii is a commensal bacterium; it is a major member of adult human microbiota and is also found in most animals. The time course of *F. prausnitzii* colonization has been described, but many questions about the specificity of the conditions required for its implantation have not been answered. The ubiquity and population level of *F. prausnitzii* and its frequent involvement in dysbiosis indicate that this bacterium is a major contributor to the functions of the microbiota and intestinal health. Modulation of *F. prausnitzii* populations may be useful for preventive or therapeutic treatments. However, it is still not clear how to treat and/or prevent IBD associated with *F. prausnitzii* dysbiosis, and it may be necessary to establish a personal diagnosis for each patient, based on microbiota analysis, to allow appropriate management (**Fig. 1**). Treatments complementary to standard therapy should be investigated, involving, for example, various nutritional strategies or prebiotics or probiotics that favor *F. prausnitzii* population expansion. Further research, and in particular work to elucidate the mutualistic interactions between *F. prausnitzii* and the host, may lead to valuable medical applications (**Fig. 1**).

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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